Hypophysectomy or Adrenalectomy?

Their Use in Management of Advanced Malignant Disease As Observed in Clinics in Europe

FRANK W. BAILEY, *M.D.*, Fresno

• **The dependence of cancer of the breast and prostate gland upon sex hormones has led to an attack on this problem by way of adrenalectomy with castration or by hypophysectomy when hormone treatment has failed. The survival period of patients who have had adrenalectomy or hypophysectomy has been prolonged by use of cortisone. The risk of either operation is reasonable and maintenance of life on cortisone is simple. The results are encouraging, with a tendency in favor of hypophysectomy. It seems justifiable to advise operation at an early stage of the disease.**

IT HAS BEEN KNOWN for some time that cancer of the breast and of the prostate gland can be controlled by the administration of sex hormones because they are hormone dependent tumors. In 1896 George Beatson,[1] an English surgeon, published the first report on the effect of the removal of the ovaries as a method of treatment of cancer of the breast. Lett[6] reported 99 cases of oophorectomy for the late stages of mammary carcinoma in 1905. During the next 50 years radiation was used to induce menopause, and oophorectomy fell into disuse. It was demonstrated by Huggins and Bergenstal[4] in 1951 that the adrenal cortical hormones sustained mammary cancer and that their withdrawal was followed by pronounced regression of the tumor. The discovery that patients who have had the adrenal glands removed can survive a long time on cortisone has been a stimulus to adrenalectomy as a method of treatment.

The work of Huggins and co-workers[3,4,5] pointed out that gonadectomy is followed by a compensatory hypertrophy of the adrenal glands and an increase in the function of the adrenal cortex, that removal of the testes in man is followed by an increase in the content of 17-ketosteroids in the urine, which can be reduced by bilateral adrenalectomy, and that after oophorectomy women continue to excrete estrogens in the urine which disappear from the urine after adrenalectomy. Gonadectomy and adrenalectomy appear to eliminate all the sources of hormones which can stimulate the growth of carcinoma of the mammary and prostate gland and to produce a physiological environment low in steroids.

Carcinomas of the breast and prostate gland sometimes are favorably affected by alterations in the hormonal environment brought about by castration, by treatment with appropriate hormones, and by adrenalectomy. The effect of the hormone treatment in these cases has been attributed to a depressing action on the hormone production of the pituitary gland. Other tumors which have been responsive to the change in the hormone medium brought about by hypophysectomy are chorionepitheliomas and malignant melanoma.

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EXPERIENCE WITH HYPOPHYSECTOMY

While visiting with a number of neurosurgeons in England and in continental Europe in 1955, the author became aware of the amount of recent work which has been done by them in connection with this problem. Olivecrona and Luft[7] at Stockholm had performed hypophysectomy in 12 cases of malignant tumor, all in advanced stage, after all other available methods of treatment had been tried and had failed. There was one case of carcinoma of the prostate gland, one of malignant chorionepithelioma, one of hypernephroma and nine cases of carcinoma of the breast. The operation was well tolerated in every case and there were no deaths or serious complications of any kind as a result of it. In the one case of cancer of the prostate, inability to urinate abated and pain disappeared within two weeks after the operation. However, symptoms reappeared after three months and the patient died. At autopsy the adrenal glands were observed to be very small and there remained small rests of regenerating hypophyseal tissue in the pituitary fossa. In most of the nine cases of carcinoma of the breast the patients had huge lesions recurrent after mastectomy, as well as pulmonary and other metastatic lesions. Five of the patients had had hypophysectomy only a short time before the author observed them—two after having had cerebellar metastatic tumors removed. All were doing well. In two cases the adrenal test indicated that functioning pituitary tissue was still present, and the patients showed no appreciable improvement. The rest of the patients were still alive, but it was felt by the surgeons that it was too early to decide on the ultimate effects of hypophysectomy since it had

been done in these cases only two or three years previously.

Hormonal control as an approach to the problem of advanced cancer of the prostate or of the breast was taken up in 1953 by Mr. Murray A. Falconer, director of Maudsley neurosurgical unit of Guy's Hospital, London. Falconer and a co-worker, Peter Schurr, had treated almost 50 patients with carcinoma of the breast or of the prostate gland, about half of them by adrenalectomy and half by hypophysectomy. At the time of the author's visit at the hospital during the summer of 1955 it seemed that the patients who had had hypophysectomy had better relief from pain and metastasis and better regression of visible and palpable lesions than the patients who had had adrenalectomy. None of the patients had been treated by x-ray or by implantation of radioactive material.

EXPERIENCE WITH ADRENALECTOMY

Sir Stanford Cade,[2] senior surgeon at Westminster Hospital, which is in no way connected with Maudsley, did bilateral adrenalectomy in 56 patients with disseminated mammary cancer in the three-year period 1953-1955. He reported an extended survival on cortisone maintenance up to 24 months. In some cases both subjective and objective improvement was obtained—relief of pain from skeletal metastasis, regression of visible and palpable lesions, and union of pathological fractures. Beneficial effect of some degree was noted in about 60 per cent of the patients, and in about 23 per cent of the patients who benefited the improvement was quite remarkable and surprising.

SELECTION OF PATIENTS

In both these series of adrenalectomy and hypophysectomy, there were widespread skeletal, visceral and soft tissue metastasis and the expectation of life was very limited. Since they were done on patients to whom nothing further could be offered, the operations were put to a very severe test. It was found that patients with disseminated disease in the pulmonary lymphatics, with involvement of the pericardium and the heart were of high operative risk and the operations were not done on such patients. In fact, involvement of the lungs and heart to any extent which impaired vital function was regarded as the main contraindication for the operation.

MANAGEMENT

In both series, before adrenalectomy with castration was done, all the patients were carefully assessed as regards the extent of the disease and the general state of health by clinical, radiological and chemical investigations. In addition, the output of 17-ketosteroids and estrogens was studied and Thorn's test for adrenocortical function was done. The preoperative preparation consisted of the correction of the state of the blood by transfusion and the administration of cortisone. In one of the series only cortisone was used. There seemed to be no need for desoxycorticosterone. Cortisone acetate was given in 100 mg. doses by intramuscular injection at periods of 38 hours, 24 hours and 1 hour before the operation.

During the operation and in the immediate postoperative period norepinephrine was used only if there was pronounced decrease in the blood pressure —as an emergency measure. On the first postoperative day cortisone was given by injection in 100 mg. doses every six hours; on the second day, 50 mg. at six-hour intervals; then from the third to the fifth postoperative day 25 mg. of cortisone acetate by mouth every six hours. The dosage then was further reduced to 75 mg. a day and finally to 50 mg. daily as a maintenance dose. Patients were often given instructions about the need of extra cortisone during intercurrent illness or following an operation or an accident.

In doing hypophysectomy the necessity of preventing brain edema of any great degree has to be considered. It is well established that corticotropin and cortisone, as well as desoxycorticosterone, bring about a retention of electrolytes in fluid. When using corticotropin and desoxycorticosterone, and to a certain degree even cortisone, this retention reaches its highest value during the first days of hormone administration and is followed by a period of increased excretion. It is advisable to perform the operation during this period of increased excretion. For one week before operation, cortisone, 50 mg. per day, and testosterone propionate, 25 mg. a day, were given.

After operation, decreasing hormone dosages were given. The permanent hormone treatment can often be prescribed from the third or fourth week on. Cortisone is then given in a dose of 12.5 mg. (½ tablet) twice daily and later on, combined with 0.2 to 0.4 mg. of thyroxin. In the series here considered, testosterone propionate was omitted in the permanent substitution therapy in order not to obscure the results in cancer of the prostate gland.

ADRENALECTOMY WITH CASTRATION

Bilateral adrenalectomy and oophorectomy can be done in one stage. The practice at present is to carry out bilateral oophorectomy and unilateral adrenalectomy in one stage and postpone the second adrenalectomy for seven days. The best approach to the adrenal gland is through the bed of the twelfth rib with the patient lying on the side in the position usually adopted for adrenal operations, either through an incision parallel with the vertebral col-

umn or a flank incision. The operation is technically simple but the adrenal gland must be handled with care, for it is friable and in some patients a pronounced fall or rise in the blood pressure occurs when the gland is manipulated. Hemorrhage is controlled by careful ligation of the adrenal veins, which show considerable anatomical variations and with which the surgeon should be familiar. Accidents which can be guarded against are injury to the pleura, to the renal vein or to the inferior vena cava. Oophorectomy is done through a lower midline abdominal incision at the time the first adrenal gland is removed. In most patients convalescence is smooth and the postoperative course gives rise to anxiety to the surgeon only in patients with cardiac or pulmonary involvement, by disease or by postoperative difficulties.

HYPOPHYSECTOMY

The pituitary region is usually exposed by a right pituitary skin and bone flap entrance, and the arachnoid membrane in the chiasmal cistern is removed as completely as possible. The pituitary stock is hidden beneath an optic nerve. The nerve is retracted with a blunt hook sufficient to expose the stock. After the pituitary stock has been exposed, silver clips are applied to it and it is divided. The diaphragm of the sella is thin around the insertion of the stock. In the periphery a venous ring of varying size can be seen and the diaphragm is opened just inside this ring. The gland is mobilized with blunt instruments. In favorable cases the entire gland can be lifted up from the sella and removed. In cases in which this cannot be done, piecemeal removal with rongeurs and spoon is carried out. Even if a tiny piece of viable glandular tissue is left behind, it may regenerate and the result will be a poor one. So far, the best method of removing pituitary remnants is to pack the sella with a cotton pledget and then inject it with Zenker's solution. This is then allowed to remain in the sella for a couple of minutes. The procedure is repeated until the lining of the sella appears thoroughly cauterized.

CONCLUSION

The surgeons in England who are systematically and extensively investigating the use of hypophysectomy and adrenalectomy in the management of advanced cancer of the prostate and the breast do not feel that they have a large enough series of cases with results from which to draw reliable statistical conclusions. However, they recognize a trend in favor of hypophysectomy. After reviewing the histories of a number of the cases in which they have used the operations, it is the author's feeling that if the regression of advanced malignant disease that was observed in these cases can be obtained by these operations, it would be worth the effort and the risks involved to intervene sooner, especially in cases where there is the earliest evidence of metastasis after mastectomy and after male hormone therapy for carcinoma of the prostate gland has failed.

301 Bank of America Building, Fulton and Tulare Streets, Fresno.

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